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Interfacing Physiologically-based Pharmacokinetic Modeling and Simulation Systems
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ABSTRACT

The graphical user interface of a physiologically-based pharmacokinetic (PB PK) modeling and simulation system developed for the Macintosh™ computer is described. The user interactively specifies: 1) the anatomical structure of the model (tissues) and the anatomical structure of each tissue; 2) physiological relationships; 3) transport characteristics; 4) thermodynamic properties of the substance.

The interface utilizes four independent interactive windows: Model, Parameter, Kinetics, and Solution. The user selects tissues for the model and an exposure route from a flow diagram consisting of nine different tissues and four possible routes of exposure, or from a menu. Assumptions limiting the rate of mass transfer can be specified for each tissue. Parameters for each tissue, as well as dosage parameters, are entered via dialog boxes. This method of specifying the model parameters encourages "What if...?" scenarios. The model is cast in an S-system format for ease of solution and for added flexibility in simulating inherently nonlinear biological systems. The system generates a steady-state solution, which can be plotted as multiple tissue concentration–time curves on a configurable graph. The data files can be exported to other graphics and statistics packages. The pictorial flow diagram, a table of all tissue parameter values, the steady-state solution set, and the graphic plots can be printed.

INTRODUCTION

Physiologically-based pharmacokinetic (PB PK) models utilize a system of lumped compartments which are designed on the basis of the actual anatomy and physiology of the species. Model parameters fall into four broad categories: 1) anatomical, e.g., organ volumes and tissue sizes; 2) physiological, e.g., blood flow rates and enzyme reaction rates; 3) thermodynamic, e.g., drug–protein binding isotherms; and 4) transport, e.g., membrane permeabilities (Himmelstein and Lutz, 1979).

The first step in the development of a PB model is to select the number and type of tissues. Once the tissues are selected, a flow scheme is drawn with the desired regions describing the species anatomically (Figure 1). The liver, gut, spleen, and pancreas (enterohepatic system) are interconnected anatomically, maintaining the physiological basis.

Each tissue is initially considered to consist of three homogeneous subspaces: (a) a vascular space through which the tissue is perfused with blood; (b) an interstitial space, which forms a matrix for the tissue cells; and (c) an intracellular space consisting of the tissue cells that comprise the organ (Figure 2).

Rate-limiting assumptions may simplify the 3-subspace model to one or two subspaces. The flow-limited model has a single space and is used to model tissues that are not well perfused by the circulatory system. The membrane-limited model assumes that the transfer across the cell membrane is rate limiting, and thus reduces the tissue model to 2 subspaces. Our system admits any of the above three configurations for a tissue. The system also permits the specification of four physiological processes which can affect the distribution and flux of a substance: transport across a membrane, binding, excretion, and metabolism. A linear or non-linear formulation can be used for modeling these processes, depending on the available information for a given process. Generally, a PB model may include any or all of these processes.

IMPLEMENTATION OF PK MODELS

Although the PB approach to PK modeling is the method of choice, there is, among some, reluctance to use this approach because of the mathematics associated with the method (D'Souza and Boxenbaum, 1988). Nevertheless, progress in the development of computer software for solving the system of differential equations generated by these models is being reported.

The literature describes three modeling methods. They include utilization: 1) of a fixed model simulator where the number and/or types of tissues are fixed (Bloch et al., 1980; Gabrielsson and Hakman, 1986; Menzel et al., 1987); 2) of a general simulation system (Blau and Neely, 1987); and 3) of spreadsheet-based simulators (Ball et al., 1985; Johanson and Näslund, 1988).

At the heart of these modeling methods are the algorithms used to solve the system of differential equations. Since algebraic solutions are not available for these complex models, they must be approximated by numerical methods. Two terms used to characterize these numerical methods are accuracy and efficiency: by accuracy is meant the error (difference) between the numerical solution and the true solution; by efficiency is meant the "cost" of the solution in terms of convergence of the estimation procedure, which is generally equated to computer time. Some of these methods are very simple, easy to program, and are efficient; their disadvantage is that they do not give very accurate results. Other methods, while achieving better accuracy, are more difficult to program and are less efficient.

The modeling system described in this paper utilizes the Power-Law Formalism (Savageau, 1969; Voit, 1991). It admits several system-modeling strategies. Table A is a mathematical representation of a generalized tissue with three subspaces, denoted by the subscripts 1, 2, and 3. This model expresses changes in mass in terms of blood and tissue concentrations, and general flux and biotransformation terms. In this representation, biotransformation (metabolism/excretion) can only occur in the "cellular" subspace. This representation also permits this set of equations to be used for modeling flow-limited and membrane-limited configurations by setting appropriate terms equal to zero.

Table B describes the characteristics of the possible tissue configurations admitted by the generalized 3-subspace model. The number of subspaces, presence or absence of biotransformation and flux terms, type of flux (ACTive or PASsive), and type of biotransformation (LINear or Michaelis-Menten) are specifically enumerated.

Table C is the S-system representation corresponding to the linear system of Table A. This set of three S-system equations can describe all possible cc.figurations for a 3-subspace tissue. In the S-system approach the different configurations are admitted by altering the values of the parameters according to the rate laws that are in effect for a particular configuration.

Our "PB-PK" modeling and simulation system is a flexible and generic PB PK modeling and simulation system developed for the Macintosh™ computer. The user interactively specifies: 1) the anatomical structure of the model (tissues) and the anatomical structure of each tissue (*i.e.*, the parameters of the vascular, interstitial, and intracellular subspaces); 2) physiological relationships (blood flow rates for each tissue, metabolism and excretion of the substance); 3) transport characteristics, which also entails identification of flow- and membrane-limitations; and 4) thermodynamic properties of the substance (tissue partition coefficients).

The graphical user interface closely adheres to the human interface guidelines proposed by Apple Computer (1987).

The application has four independent interactive windows: **Model, Parameter, Kinetics,** and **Solution.** The content of each window can be printed, and the model (including parameters) and simulation data (sim-data) saved independently as files. The sim-data file format allows it to be exported to other graphics and/or statistical applications.

The user defines the anatomical model in the Model window (see Figure 1). This requires selection on a flow diagram consisting of a subset of the nine different tissues identified in the window: lung; heart; liver; gut; spleen; kidney; muscle; testes; and "other". There are four possible routes of exposure: intravenous (IV), intramuscular (IM), oral, and inhalation.

Parameters for the tissues are entered by means of dialog boxes (Figure 3). The user chooses the tissue configuration, depending on rate-limiting assumptions. The number of parameters to be specified in the dialog box is a function of this selection. An array showing the values of all the model parameters is displayed in the Parameter window.

Exposure route parameters are also entered *via* a dialog box. The dosage regimen (Figure 4) admits a bolus or continuous dose, with the user able to specify the time at which the dosing occurs, as well as the fraction, F, that is absorbed into the blood. Because of the modular format used in the development of this software, it will be possible to incorporate more complicated dosing regimens (*e.g.*, the universal elementary dosing regimen (Sebalt and Kreeft, 1987))

The Kinetics window (Figure 4) displays the results of the simulation once the model has been selected and the parameters entered. Dialog boxes are linked to this window to allow for configuration of the graph (time in hours/days,

selection of which tissues or metabolites to graph, *etc.*), plotting of experimental data, and for any other parameters needed for solution of the set of differential equations.

The Solution window displays the resulting simulation data in a columnar format. The user can specify the frequency with which the time points are displayed (*e.g.*, every sixth time point).

The set of differential equations generated by the selection and specification of tissues are solved by incorporating the necessary modules from ESSYNS™, an interactive program written for the analysis of mathematical models expressed in S-system form (Irvine and Savageau, 1990; Voit *et al.*, 1989).

DISCUSSION

As in all simulation systems, our modeling system is dependent on external estimation of PK parameters used in the model. These estimates may be derived from: the literature; the investigator's previous experience; classical parameter estimation experiments; or reflect a hypothesized value. Although many physiological parameters are available in the literature, others, such as binding constants, frequently are not. When experimentation is not possible in humans the investigator must rely on *in vitro* or animal studies.

PB PK models are attractive for a number of reasons. First and foremost they are physiologically and anatomically correct. Second, they admit non-linear relationships. Third, they may be cast in the form of S-systems, thus making them mathematically tractable. Fourth, these systems may be easily modeled using our system. Finally, these models may be used to visually describe system dynamics and status through the graphical user interface. The classical approach to PK modeling relates dose and plasma concentration. The physiological approach goes one step further to relate dose, plasma, and tissue concentrations (Ritschel and Banerjee, 1986). Furthermore, it is adaptable to changing physiological circumstances and can allow for species-to-species and even subject-to-subject differences within the context of the physiological or anatomical parameters in the model (Himmelstein and Lutz, 1979). Perturbation of a particular parameter allows one to predict the changes in distribution or disposition of the drug during disease states, for instance, or in the presence of another drug. The combined effect of a number of complex inter-related processes can also be determined provided sufficient data are available (Ritschel and Banerjee, 1986).

SUMMARY

Physiologically-based pharmacokinetic modeling is rapidly gaining acceptance as a method for simulating tissue drug concentrations based on anatomical and physiological parameters and thermodynamic properties of the drug. Currently available software systems that use the physiologically-based philosophy are limited by the assumption of a particular type of physiologically-based model. Using a simulation language to define a complex model can be tedious. The Janszen-Miller "PB-PK" system is an interactive

generic physiologically-based pharmacokinetic model-ing and simulation system wherein specification and modification of the model is facilitated by the graphical user interface of the Macintosh™ computer. It allows great flexibilty in specifying a model, as well as ease of specifying the model parameters, and encourages "What if...?" scenarios.
The user selects tissues for the model and an exposure route from an anatomical flow diagram or from a menu. Assumptions limiting the rate of mass transfer can be specified for each tissue. Parameters for each tissue, as well as dosage parameters, are entered via dialog boxes. The model is cast in an S-system format for ease of solution and for added flexibility in simulating inherently nonlinear biological systems. The system generates a steady-state solution, which can be plotted as multiple tissue concentration-time curves on a configurable graph. The system allows one to examine concurrent concentrations of a substance and its metabolite(s) within vascular, interstitial, and cellular components of a single tissue or organ; plot these values over time in the presence of single or repeated dosing; plot experimental data; and to generate data files for export to other graphics and statistics packages. The pictorial flow diagram, a table of all tissue parameter values, the steady-state solution set, and the graphic plots can be printed.

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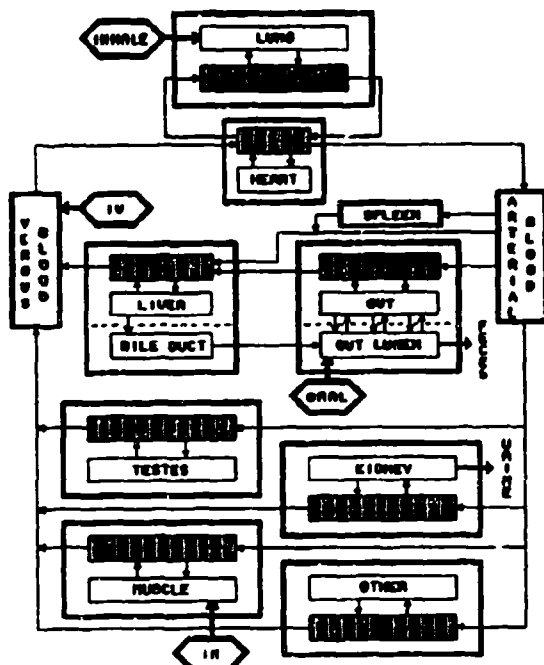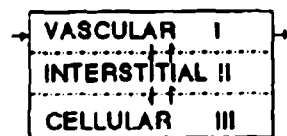
Figure 1. Flow scheme of a generic PB PK model

Figure 3. Tissue parameter dialog box.

Figure 2. Generalized 3-subspace tissue.

$$V_1 \dot{C}_1 = Q\left(C_p - \frac{1}{R}C_1\right) - \eta_1 - \tau$$

$$V_2 \dot{C}_2 = \eta_1 - \eta_2 - \tau$$

$$V_3 \dot{C}_3 = \eta_2 - \tau$$

Table A. Mathematical representation for a general 3-subspace tissue. ($\dot{C} = dC/dt$; $V =$ volume, $R =$ partition coefficient; $\eta =$ general flux term; $\tau =$ general biotransformation term; $p =$ plasma; 1,2,3 = subspace).

Number of subspaces	FLUX I→II	FLUX II→III	BIOTRANSFORMATION I	BIOTRANSFORMATION II	BIOTRANSFORMATION III
1	—	—	—	—	—
1	—	—	LIN	—	—
1	—	—	MM	—	—
2	PAS	—	—	—	—
2	PAS	—	—	LIN	—
2	PAS	—	—	MM	—
2	ACT	—	—	—	—
2	ACT	—	—	LIN	—
2	ACT	—	—	MM	—
3	PAS	PAS	—	—	—
3	PAS	PAS	—	—	LIN
3	PAS	PAS	—	—	MM
3	PAS	ACT	—	—	—
3	PAS	ACT	—	—	LIN
3	PAS	ACT	—	—	MM
3	ACT	PAS	—	—	—
3	ACT	PAS	—	—	LIN
3	ACT	PAS	—	—	MM
3	ACT	ACT	—	—	—
3	ACT	ACT	—	—	LIN
3	ACT	ACT	—	—	MM

Table B. Enumeration of biological processes for all possible configurations of a tissue. (See text for details; a dash indicates a process does not occur)
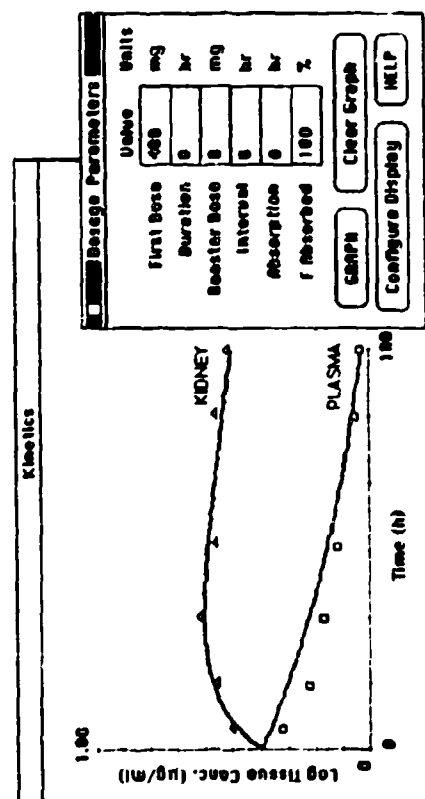

Figure 4. Dosage parameter dialog box (active) and Kinetics window (inactive) showing results of simulation (solid lines) and plotted experimental data (□ and △).

$$\dot{X}_1 = \alpha_1 X_p^{g_{1p}} X_2^{g_{12}} - \beta_1 X_1^{h_{11}}$$

$$\dot{X}_2 = \alpha_2 X_1^{g_{21}} X_3^{g_{23}} - \beta_2 X_2^{h_{22}}$$

$$\dot{X}_3 = \alpha_3 X_2^{g_{32}} - \beta_3 X_3^{h_{33}}$$

Table C. S-system representation for a general 3-subspace tissue. (g_{ij}, $h_{ij} =$ kinetic order for all processes from jth space to ith space; $\alpha, \beta =$ rate constants; $p =$ plasma; 1,2,3 = subspace)